J. Phys. Chem. A **2006,** *110,* 11151−11159

Theoretical Insights, in the Liquid Phase, Into the Antioxidant Mechanism-Related Parameters in the 2-Monosubstituted Phenols

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Received: March 20, 2006; In Final Form: July 12, 2006

The paper describes a DFT/B3LYP study, in the liquid phase, [using the PCM continuum model] on the O−H bond dissociation enthalpy (BDE) and ionization energy (IE) parameter values of the 2-monosubstituted phenols (2-X-ArOH), related to the H-atom transfer (HAT) and single-electron transfer (SET) mechanisms. The solvent and substituent effects on the conformers, the BDEs, and the IEs were studied using four electron-donating (EDG) and five electron-withdrawing (EWG) groups, in seven different solvents. In both the EDG- and/or EWG-substituted species of the parent compounds, radicals, and/or cation radicals, the most stable conformer is varied, depending on the medium and the substitution. The EWG-substituents increase IEs, resulting in a weaker antioxidant activity than the EDG ones; the effect appears stronger on the IEs than on BDEs. However, although the liquid-phase IEs, which are related to solution-phase oxidation potentials, decrease with the polarity and/or the hydrogen-bonding ability of the solvent, the opposite holds true for the BDEs, exhibiting a weaker effect. The gas-phase-calculated IE for benzene is among the most accurate ones in the field, compared to the experiment, that for phenol being the most accurate. In addition, calculated IEs for the 2-X-ArOH are in close agreement with the very few existing experimental ones. It is shown that the oxidation potentials are (a) highly correlated with the gas-phase ones, and (b) strongly solvent dependent. The stabilization/destabilization of the cation radical (SPC) contribution, in all media, is the decisive factor in the ΔIE calculation. The reasonable correlations found between the ΔBDE and ΔIE could account well for the assumption of the simultaneous action of both mechanisms in the 2-X-ArOH, in both the gas and the liquid phase. It seems, however, that the presence of a particular solvent by itself is not sufficient enough for the HAT to SET transition. The involvement of specific ED and/or EW groups in the 2-X-ArOH seems also necessary. It appears that our theoretical approach is not only generally applicable to the set of substituents important to antioxidant activity but also useful in (a) the rational design of phenolic antioxidants and (b) affording accurate BDE and IE parameter values related to both possible antioxidant mechanisms.

Introduction

Natural and synthetic antioxidants have attracted much attention over the years due to the protection of vital cell components from oxidative stress,[1] caused by the free radicals. Free radicals are involved, through chain-reactions, in a number of diseases, i.e., atherosclerosis, coronary heart diseases, and certain forms of cancer.[2,3] Chain-breaking antioxidants constitute an important class of compounds in chemistry and biochemistry of human health.[4] The most important chain-breaking antioxidants are the substituted phenols (ArOH), which inhibit oxidation by transferring their phenolic H atom to a chain-carrying peroxyl radical (ROO$^\bullet$) at a rate much faster than that of chain propagation.[4] This yields a nonradical product (ROOH) that cannot propagate the chain reaction (eq 1):

$$\mathrm{ROO^\bullet + ArOH \rightarrow ROOH + ArO^\bullet} \qquad (1)$$

It is proposed[4] that chain-breaking antioxidants can play their protective role via two major mechanisms. In the first one, the phenolic H atom is transferred in one step, as shown in eq 1, and is referred to as the H-atom transfer (HAT) mechanism.

The second mechanism, referred as single-electron transfer (SET), takes place in two steps (eq 2 and eq 3):

$$\mathrm{ROO^\bullet + ArOH \rightarrow ROO^- + ArOH^{+\bullet}} \qquad (2)$$

$$\mathrm{ArOH^{+\bullet} \rightarrow ArO^\bullet + H^+} \qquad (3)$$

$$\mathrm{ROO^- + H^+ \rightarrow ROOH} \qquad (4)$$

In the first step, the ArOH becomes a cation radical, by giving an electron to ROO$^\bullet$ (eq 2). In the second one, there is a rapid deprotonation of ArOH$^{+\bullet}$ (eq 3), followed by the protonation of ROO$^-$ (eq 4).

In the former mechanism, the bond dissociation enthalpy (BDE) of the phenolic O−H bond is the important parameter in evaluating the antioxidant action; the lower the BDE value, the easier the dissociation of the phenolic O−H bond and the reaction with the free radicals. In the SET mechanism, the ionization energy (IE) is the most significant parameter for the scavenging activity evaluation; the lower the IE value, the easier the electron abstraction and the reaction with free radicals. Moreover, the proton affinity (PA) of the radical evaluates the second deprotonation step. In recent papers,[5,6] it was shown that, in the gas phase, this step is not a rate-controlling one for the 2-, 3- and 4-X-ArOH to scavenge free radicals. In any case,

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10.1021/jp061718p CCC: \$33.50

both the HAT and the SET mechanisms must always occur in parallel, but with different rates.[4]

To perform a systematic theoretical study on both antioxidant mechanisms in the liquid phase, it is desirable to accurately determine both the BDE and IE (oxidation potential) parameters, along with those in the gas phase, for comparison.

Although a good knowledge of the antioxidant mechanism is a prerequisite in an attempt to understand the way that antioxidants act, there is not a lot of theoretical work on this particular field. Wright et al.,[4] who used the DFT approach to determine accurate BDE and IE values of phenols, reported the first thorough work in the gas phase. The authors also suggested the theoretical criteria to determine the dominant mechanism occurring in the reactions of phenolic antioxidants with free radicals. Moreover, Fox et al.[7] used DFT in an attempt to determine whether a biochemical reaction mechanism proceeds via atom transfer or electron transfer. Recently, Leopoldini et al.[8,9] studied a series of phenols and flavonoids at the DFT level to specify whether the antioxidant activity of these compounds proceeds via HAT or SET, in the gas phase, and, for the first time, in two solvents (water and benzene).

In addition, since 2001, Wright et al.[4] have identified the need of introducing a solvent model into the calculations to verify whether the gas-phase results are also relevant to reaction in solution. This, due to the biological role that antioxidants serve, constitutes one of the main targets of the present study, which may serve in the design of an optimum synthetic antioxidant. Furthermore, the expectation[4] that the SET mechanism would be strongly solvent dependent, whereas the effect in HAT would be much weaker than in the case of SET, raises another point to be answered in this work.

As a part of a continuing investigation of the structure−activity relationships on phenolic antioxidants,[10−15] we have embarked on a project to determine the BDE and IE values of 2-monosubstituted phenols, 2-X-ArOH, in both the gas and the liquid phase. The latter phenols constitute the model compounds of phenolic or flavonoid antioxidants; still, for a rational design of efficient phenolic chain-breaking antioxidants, one must consider the BDE and IE first.[16] The selection of the 2-X substitution is justified, because (a) the catechol moiety, 2-OH−ArOH, is necessary for most natural antioxidants to enhance their activity[17−20] and (b) the 2-X-ArOH could represent prototypal hydrogen bond (HB) interactions, which may be found in biological systems.[21]

On the other hand, the qualitative and quantitative knowledge of the way that each substituent contributes to the BDE and IE values seems desirable. For this reason, a variety of substituents, involving both electron-withdrawing [$-NO_2$, −CN, −CHO, and −COOH, (EWG)] and electron-donating [−Me, −OMe, −OH, $-NH_2$, and $-NMe_2$, (EDG)] groups, frequently encountered in ArOH, was selected. Furthermore, to simulate different environmental situations, seven dielectric media, ranging from strong polarity (water, ethanol, and methanol), via dipolar aprotic (acetonitrile and acetone), to the nonpolar (*n*-heptane and benzene) ones, were examined.

To accomplish this goal, the widely used DFT level of theory with the B3LYP functional was employed, along with the polarizable continuum model PCM, at the same level of theory, for the treatment of the solvent effects. It is worth mentioning here that apart from the latter model, solvent and H-bonding effects have been studied, by considering[22−29] either the specific interactions between the solvent and the substituent and/or the interaction of the solute with, for instance, 2−6 solvent molecules.

Method of Calculation. The methodology used for the accurate estimation of BDE values in the gas and the liquid phase was given in detail, elsewhere.[14] Hence, we review only the essential details needed to obtain accurate IE values in both phases.

All calculations were performed using the density functional theory,[30] as implemented in the Gaussian 98 program suite.[31] Becke's 3-Parameter hybrid functional combined with the Lee−Yang−Parr correlation functional, abbreviated as B3LYP level of density functional theory,[32] with the 6-31+G(,3pd) basis set[15] were used.

The geometries of all species were fully optimized, and all structures were true minima on the calculated potential surface, verified by final frequency calculations that provide energy minima with certainty. UB3LYP was used for the geometry and vibrational frequency calculations of the radicals ($ArO^\bullet$ and $ArOH^{\bullet+}$) and the hydrogen atom. Both the phenols and the respective radicals are calculated at the same level of theory[15,33] in all media.

Solvent effects were introduced in the calculations within the framework of the polarized continuum model[34] in its original dielectric formulation, D-PCM. The default UAHF[35] set of solvation radii was used along with a cavity described by a different number of tessarae, depending on the solute and solvent, with an average area of 0.4 Å^2.[15] A wide spectrum of dielectric constant, ϵ, values was used, ranging from 0 (*n*-heptane) to 78.39 (water), to simulate the influence of seven solvents, which, based upon their Dimroth and Reichardt's,[36] E_N^T and Kamlet−Taft,[37,38] α polarity parameter values could be divided into three groups:[15,21] *n*-heptane and benzene (group A), acetonitrile and acetone (group B), and water, ethanol, and methanol (group C).

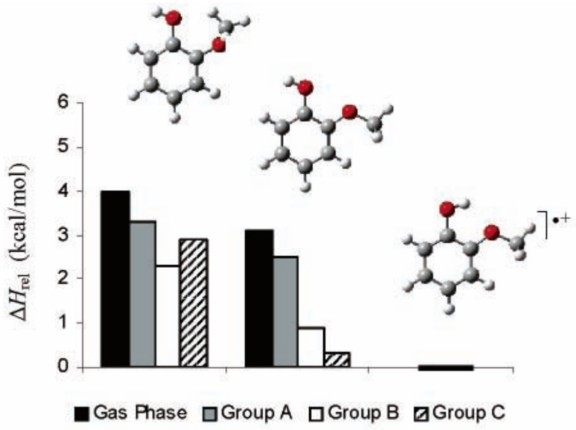
In addition, because DFT methods are also effective to calculate the IE values,[4,16,39−41] the adiabatic ones at 0 K, in both the gas and the liquid phase, were calculated as the energy difference, E_0, between the optimized parent (ArOH) and cation radicals ($ArOH^{\bullet+}$). The E_0 values were obtained as the sum of the electronic energies and the scaled zero-point energies, ZPEs, with a scale factor of 0.9810.[15]

The $\langle S^2 \rangle$ values, calculated for all 2-X-ArO$^\bullet$ and 2-X-ArOH$^{\bullet+}$ of the present study, range from 0.78 to 0.79, which are close to the expected value for a pure doublet wave function, 0.75. Therefore, the results of our DFT calculations are less affected by spin contamination in the gas and the liquid phase. These, in turn, could be reflected to the computed energies, affording accurate absolute and relative liquid-phase BDE and oxidation potential values.

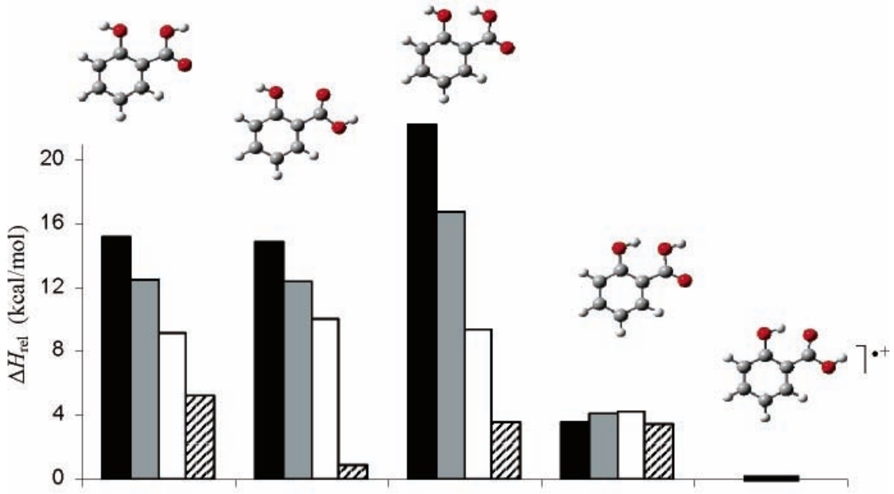
Results and Discussion

Conformers of 2-X-ArOH$^{\bullet+}$ in the Gas and the Liquid Phase. Prior to the examination of the structure and energetics of the cation radical, 2-X-ArOH$^{\bullet+}$, conformers, a short reference to those of the corresponding parent and radical compounds is provided, for comparison.

In a recent paper[14] it was shown that (i) the stability of the conformers of the parent phenols, 2-X-ArOH (X = EDG/EWG) as well as their respective radicals, 2-X-ArO$^\bullet$, changes with the environment, (ii) depending on the medium, their enthalpy differences, ΔH_{rel}, (with respect to the most stable conformer) range from 0.5 to 12 kcal/mol, and (iii) the use of the appropriate parent/radical conformer pairs[14] yields accurate calculated BDE values. Moreover, in both the gas and the liquid phase, it was also shown[14,15] that the most stable parent conformer was the *toward*, in all of the 2-X-ArOH studied, forming a HB between



2-OMe



2-COOH

Figure 1. Relative enthalpies, ΔH_{rel}, with respect to the most stable conformer of the 2-OMe- and 2-COOH−ArOH$^{\bullet+}$ cation radical conformers in each medium.

the phenolic O−H group and the 2-X one (X being either one of the −OH, −OMe, and/or the −NO_2, −CHO, and −COOH). However, the present study shows that the most stable parent conformer for the 2-Me-ArOH and 2-NH_2−ArOH, is the *away* one, (the phenolic O−H group is pointing away from the 2-substituent, in all media). In particular, the stability of the former is based mainly on steric effects, whereas that of the latter on the "reverse" HB,[14,21] formed between the hydrogen atom of NH_2 and the phenolic oxygen. On the contrary, in the 2-CN−ArOH, the most stable conformer, in the gas phase and in group A, is the hydrogen-bonded *toward* one, whereas in groups B and C, it is the *away* one. Moreover, for the 2-NMe_2−ArOH, the *toward* is the most stable conformer in all media. Finally, the hydrogen-bonded *toward* is the most stable parent conformer, for some of the 2-X-ArOH (X = −F, −Cl, −Br, and −CF_3), in the gas phase.

For the radical conformers, 2-X-ArO$^\bullet$, it was shown[14] that the most stable one either forms a "reverse" HB, between the hydrogen atom of the substituent and the phenolic oxygen atom (e.g., 2-OH−ArO$^\bullet$) or a HB is not formed, due either to the long distance (e.g., 2-CHO−ArO$^\bullet$) or to steric effects (e.g., 2-Me-ArO$^\bullet$). Moreover, some radicals (e.g., 2-NO_2−ArO$^\bullet$) present only one conformation. All of the 2-X-ArO$^\bullet$ studied herein showed the same picture.

The study of the conformations of all short-lived 2-X-ArOH$^{\bullet+}$ cation radicals, in solution, and their stability differences between the gas and the liquid phase that follows is attempted for the first time.

Figure 1 represents the stability of the conformations of two cation radicals only, being an EDG-substituted (−OMe) and an EWG one (−COOH). In this figure, the relative enthalpies, ΔH_{rel}, of all possible conformers, derived in each medium, are shown with respect to the most stable one (considered to be at the zero level). The analogous stabilization scheme for the rest cation radicals (drawn for all 2-X groups, in all media) can be found in the Supporting Information (Figure S1).

Figure 1 shows that the most stable 2-OMe-ArOH$^{\bullet+}$ conformer is the *toward*, hydrogen-bonded one, in all media, whereas (i) the most energetically unfavored one is the *away* (in which the methoxy group is twisted out of plane) and (ii) the planar *away*, non hydrogen-bonded one, lies between them, in all media. Nevertheless, the stability of the latter increases on going from the gas phase to group C, (evidenced by the ΔH_{rel} values, ranging from ca. 4 to ca. 0.5 kcal/mol, respectively). Similar to the EDG-substituted 2-OH-parent phenol, the most stable EDG-substituted cation radical, in all media, is the *toward* hydrogen-bonded one. Unlike the previous ones, for the 2-Me-ArOH$^{\bullet+}$, the *away* is the most stable conformer, (see Figure S1) for steric reasons. The same holds also true for the 2-NH_2−ArOH$^{\bullet+}$, in which only the *away* conformer (possessing a "reverse" HB) was detected on the potential energy surface. Moreover, for the 2-NMe_2−ArOH$^{\bullet+}$, in contrast to the corre-

TABLE 1: B3LYP/6-31+G(,3pd)-Calculated BDE Values for the 2-X-ArOH in the Gas and the Liquid Phase (in kcal/mol)

X	gas phase	*n*-heptane	benzene	acetone	acetonitrile	ethanol	methanol	water
H	88.5	90.1	90.1	90.9	91.5	95.9	95.9	96.7
NO_2	103.3	103.3	103.6	101.2	101.5	99.4	99.2	99.4
CN	92.2	92.9	92.9	93.0	93.5	97.0	97.0	97.8
CHO	97.4	98.2	98.6	97.8	98.3	98.6	98.5	99.1
COOH	95.7	96.0	96.0	94.8	95.2	97.4	96.8	97.3
Me	86.9	88.2	88.3	88.6	89.1	91.6	91.6	92.3
OMe	81.8	84.3	84.6	88.4	88.5	89.7	89.5	90.0
OH	81.7	83.6	83.6	84.8	85.4	89.0	89.0	89.8
NH_2	78.4	79.6	79.7	79.7	80.1	82.5	82.5	83.2
NMe_2	81.0	81.3	81.1	80.5	80.8	83.2	83.0	83.2

sponding parent one, the *away* conformer was found to be energetically favored, relative to the *toward* one,[42] in all media. Finally, like the parent phenols, the relative stability of the most stable cation radical conformers decreases, on going from the gas phase and/or apolar solvents to the polar or the protic ones; 2-Me-ArOH$^{\bullet+}$ is the only exception, presenting the reverse order.

The most stable conformation of 2-COOH−ArOH$^{\bullet+}$ (Figure 1) is the hydrogen-bonded *toward* one (in which the HB is formed between the phenolic O−H and the C═O of the substituent), whereas the most unfavorable one changes with the medium. Moreover, in group C, the ΔH_{rel} value differences between the most stable *toward* and the most stable *away* conformations becomes small. Unlike the EWG-substituted parent phenols, the majority of the corresponding cation radicals present a change in the most stable conformer in the protic solvents (Figure S1). For instance, the *toward* 2-NO_2−ArOH$^{\bullet+}$ is the most favorable conformer in the gas phase and in groups A and B, and the same holds true for the *away* one in group C (Figure S1). Hereafter, in the calculation of the BDE and IE values, the most stable conformer of each species (parent, radical, and/or cation radical) is carefully selected, because it is varied depending on the medium.

DFT-Computed BDEs and IEs of Ortho-Substituted Phenols. The determination of reliable BDEs and IEs of 2-X-ArOH, in both the gas and the liquid phase, is a prerequisite in our attempt to shed light on the kind of mechanism favored in each medium. The O−H BDEs, summarized up to 1997 by dos Santos and Simoes,[43] along with a recent review[44] and a number of computational studies in this field,[4,8,9,16,26] comprise an efficient benchmark of literature data. However, a few of them only refer to solution-phase BDEs.[8,9,45] Moreover, the BDE of phenol provides a reference value for all phenolic antioxidants, and its value was recently critically re-evaluated.[46,47]

Comparisons between the available experimental or theoretical BDEs with the calculated values for the 5 out-of-the 10 2-X-ArOH presented herein were made in recent papers.[14,15] The computed results for the gas- and the liquid-phase BDEs of the selected 2-X-ArOH are reported in Table 1. All BDEs refer to the lowest energy conformers, being either the *toward* or the *away* one, with respect to each medium. It can be seen that (i) the EWG increase the O−H BDE relative to phenol, whereas the EDG present the opposite effect and (ii) the stronger the electronic effect of the substituent the more substantial the change on the BDE value. In particular, in the gas phase, the O−H BDE decreases by ca. 25 kcal/mol, on passing from the $-NO_2$ (EWG) to the $-NH_2$ (EDG). Moreover, the substituent effect on the BDEs decreases in solution, on going from the apolar solvents (ca. 24 kcal/mol) to groups B (ca. 21.5 kcal/mol) and C (ca. 16.5 kcal/mol). A possible rationale for this could be the unequal stabilization/destabilization of the parent molecule and the respective radical in one solution to the other (see also the discussion in the next section). Because the larger the liquid-phase BDEs the weaker the antioxidant activity, all of the EWG-substituted phenols should present a weaker antioxidant activity than the EDG ones in all media.

In addition, an inherent solvent effect, denoted by the larger, than the gas phase, BDEs in solution, appears for all but the 2-NO_2- (in groups B and C) and the 2-NMe_2- and 2-COOH−ArOH (in group B). Moreover, on going from group A to C, the solvent effect increases with the polarity and the hydrogen bonding ability of the solvent, and a similar effect is observed for solvents belonging to the same group, noted also before.[14] Hence, the more polar or protic the solvent, the more difficult for the hydrogen atom to be abstracted. It is also seen that the EDG-substituted phenols present a larger solvent effect, ranging from ca. 1.0 to 8.0 kcal/mol, compared to the weaker effect of the EWG-substituted ones, (ranging from ca. −4.0 to 2.0 kcal/mol). The above differences in the solvent effect could be attributed[14,15] to the stronger intramolecular HBs in the 2-EWG substitution than in the EDG one.

It is seen that in group C, a solvent effect on the BDEs of as much as 8 kcal/mol was computed for some phenols, in agreement with analogous data[9,29] found in water. Moreover, in ref 23, the solvation effect on PhO−H BDE is estimated as 5−9 kcal/mol, depending on the theory level (assuming that a cluster with 4 water molecules simulates solvation). In ref 24, the value is in the 7−10 kcal/mol range. Our value is 8.2 kcal/mol. Therefore, although authors in ref 24 determined their value using phenol-$(H_2O)_{1-6}$ clusters (hence, they considered only interactions of the solute with a few water molecules in the first coordination shell), they achieved agreement with PCM. Moreover, an overestimation by about 9 kcal/mol was derived between our method and that (HB model) of Guerra et al.[48] This could be due to the fact that the PCM approach takes into account both the solvent−substituent solvation effects (first solvation shell) and the long-range dipole−solvent interactions, whereas the HB model considers that in phenol there is only a HB interaction between the H atom of the hydroxyl group and the O atom of water. Guerra also considered the solvation of the radical. Hence, their problem could be related to the fact that although the cage structures in their paper are more stable structures than the clusters in refs 23 and 24, their calculation involves only two water molecules, neglecting the effect of the other water molecules. The number of molecules in the cluster may be much less important in other solvents but probably not in water. Nevertheless, our BDE_{sol} of PhO−H in MeOH is in close agreement with the theoretical one found by Estacio et al.[22] This is also the case with our values in benzene and acetonitrile, compared to those of Correia et al.[49] and Guedes et al.[28] Moreover, our results for the BDE_{sol} of PhO−H in benzene, *n*-heptane, and acetonitrile are in close agreement with the corresponding experimental data[25,26,28] of 90.5, 89.4 (isooctane), and 92.9 kcal/mol, respectively. This is also the case with our value for the catechol in acetonitrile.[26]

TABLE 2: Experimental and Calculated Gas and Liquid-Phase Ionization Energies at 0 K for 2-X-ArOH (in kcal/mol)

X	exp[a,b]	gas phase	*n*-heptane	benzene	acetone	acetonitrile	ethanol	methanol	water
H	195.8	194.1	171.0	167.4	148.3	147.3	141.6	141.1	140.0
NO_2	209.8	211.1	189.7	186.5	167.6	166.7	157.1	153.2	155.4
CN		206.9	183.1	179.4	159.1	157.9	151.6	150.9	149.5
CHO		200.2	178.8	175.6	157.2	156.3	151.4	150.8	149.8
COOH		197.8	176.8	173.4	155.8	154.7	149.9	149.2	148.2
Me	187.7	188.1	166.6	163.3	144.8	143.8	138.8	138.3	137.3
OMe		180.6	160.5	157.4	140.3	139.4	133.8	133.2	132.2
OH	187.9	187.5	164.9	161.3	142.5	141.4	135.7	135.3	134.5
NH_2		168.7	147.9	144.4	126.9	125.9	121.0	120.6	119.4
NMe_2		157.2	137.5	135.3	120.8	117.8	114.5	117.9	113.1

[a] Experimental data from NIST Database (National Institute of Standards and Technology on-line database. Standard reference Data Program 69, June 2005 Release. http://webbook.nist.gov). [b] Calculated IE values, in the gas phase, for the X = Br and Cl-substituted 2-X-ArOH are: 196.8 and 199.1, compared to the available experimental ones of 209.8 and 214.0, respectively.

To check the accuracy of the derived IE values, our B3LYP/6-31+G(,3pd)-calculated[15] IEs of phenol and benzene (commonly used as reference compounds[7,41]) in the gas phase are compared with the available experimental ones.

For our gas phase, the calculated IE (208.4 kcal/mol) for benzene is better than that obtained from the HF, MP2, and PMP2 methods.[40] The deviation from the experimental IE (213.2 kcal/mol)[50] is only 2.3%. Moreover, the resulted IE values[40] by using the B3LYP method with a variety of basis sets [from the smallest 6-31G(d) to the largest 6-311G(3df,3pd)] were all lower than 207.6 kcal/mol. The only exception was that of the 6-311++(3df,3pd) basis set,[40] presenting a better approach (∼209 kcal/mol) with the experiment. Furthermore, recently, Wright et al.[51] proposed a “universal” method (MLM2) for the study of the molecular properties in the gas phase. In that work, by setting the H-atom energy to its exact value of $-0.5E_h$ rather than the computed one, the IE value of benzene was computed to be 209.7 kcal/mol.

Our gas-phase-calculated IE for phenol (194.1 kcal/mol) is better than those (184.1[41] and 184.9[16] kcal/mol) derived using other DFT methods. The deviation from the experimental IE (195.8 kcal/mol) is only 1%. The calculated IEs for phenol (192.7 kcal/mol) and catechol (184.5 kcal/mol) by Wright et al.[51] were considered to be the best in the field. It appears that our corresponding values lie closer to the experiment than the aforementioned ones.

The gas- and liquid-phase-calculated IE values for all of the 2-monosubstituted phenols studied, are listed in Table 2 along with the available experimental ones. It should be mentioned that, with the exception of catechol,[16,51] theoretical IEs are not available in the literature neither in the gas nor in the liquid phase. Hence, our calculated IEs constitute the first predictions in both phases.

An inspection of the numbers appearing in Table 2 show that, with the exception of 2-Br−ArOH and 2-Cl−ArOH, the calculated gas-phase IEs are in very good agreement with the available experimental ones. This disagreement is expected because these two values were determined using the electron impact studies,[52] an experimental technique that was shown to predict ionization energies, which are typically too high.[41,53]

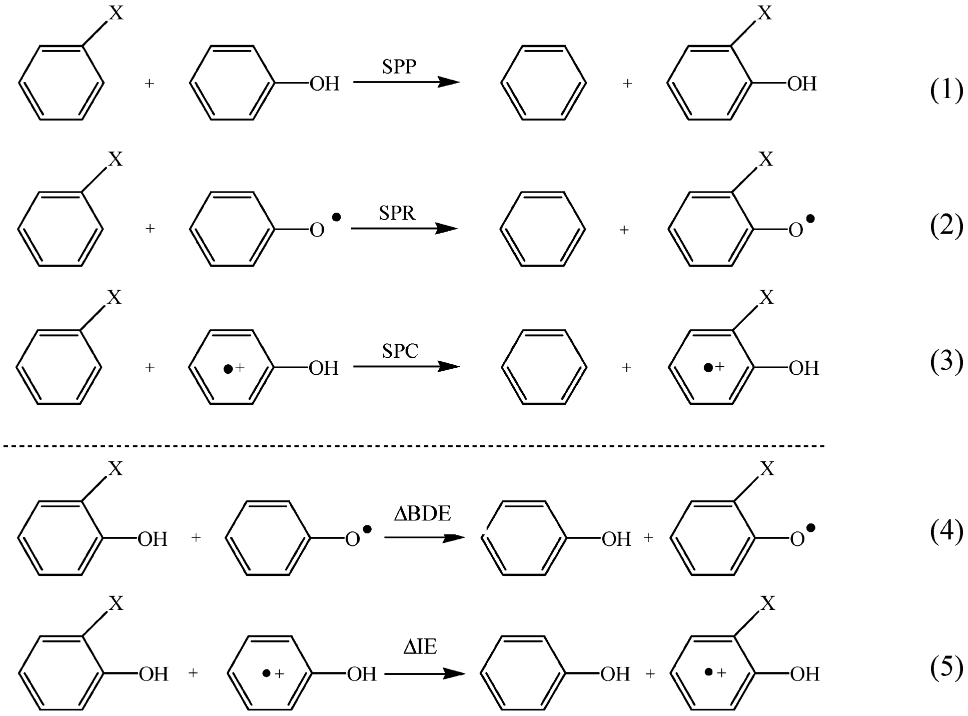
Similar to the BDE values, the EWG increases the IEs relative to phenol, whereas the EDG presents the opposite effect, in both the gas and the liquid phase. Moreover, the change on the IEs becomes more significant as the EWG and/or EDG becomes stronger. In particular, on going from the strongest EW group, $-NO_2$, to the strongest ED group, $-NMe_2$, the IEs decrease by ca. 54 (gas phase), 52 (group A), 48 (group B), and 40 (group C) kcal/mol. The substituent effect on the IE appears stronger than the one on the BDE and decreases slightly in the protic solvents. Because the larger the IEs the harder the electron abstraction, all of the EWG-substituted phenols should present harder electron abstraction than the EDG ones and, hence, a weaker antioxidant activity.

Furthermore, the solvent effect on the IE seems to possess an opposite trend compared to that on the BDE. In particular, although the oxidation potentials appear different than the gas-phase ones, denoting an inherent solvent effect, their values decrease on going from the gas phase to group C. Moreover, the oxidation potentials for each phenol are almost the same for solvents belonging to the same group, and the relative differences become significant on going from group A to C (the most important change occurs on going from group A to B). In particular, the oxidation potential of phenol decreases, relative to the gas phase, by ca. 13% (25 kcal/mol) in group A and by ca. 24% (46 kcal/mol) and ca. 27% (53 kcal/mol) in groups B and C, respectively. Furthermore, the solvent effect appears stronger in the IEs than in the BDEs (Tables 1 and 2), being 3-fold larger than the one on the BDE (corresponding increases range from ca. 2 to ca. 9%), for either the EDG- and/or the EWG-2-monosubstituted phenols. This verifies the assumption made by Wright et al.[4] that the oxidation potentials would be strongly solvent dependent, due to the solvent stabilization of the charged species. In addition, this is also the case with their assumption that the oxidation potentials in solution will be highly correlated with the gas-phase ones. As a matter of fact, the regression coefficient, R^2 values ($n = 10$), derived from the correlation between the calculated gas-phase IE values and the liquid-phase ones, are: 0.9974 (*n*-heptane), 0.9965 (benzene), 0.9878 (acetone), 0.9906 (acetonitrile), 0.9876 (ethanol), 0.9513 (methanol), and 0.9752 (water).

It was shown recently[14] that reasonable correlations exist between the BDE[54] and solvent and/or solute parameters. Hence, the correlations of both BDEs and oxidation potentials in solution, with six solvent parameters, are examined next for all of the 2-X-ArOH studied. In particular, three solvent parameters[38] are selected, representing physical properties, being the dielectric permittivity, ϵ, the Kirkwood function, f_ϵ , of the latter and the dipolar moment, μ, as well as three additional ones, representing chemical solvent properties, being the Dimroth and Reichardt’s, $E_N{}^T$,[36] polarity parameter value, and the a and β Kamlet−Taft polarity parameter values[32,38] (a refers to the Lewis acidity and β to the Lewis basicity of the solvent).

The correlations of the BDEs of all of the 2-substituted phenols with the above solvent parameters appeared better (Table S1) for those representing the chemical properties. In particular, the best correlation was shown by the a polarity parameter value [with reasonable correlation coefficient, r, values ranging from 0.878 to 0.996 for the 10 phenols ($n = 10$)][55] and the $E_N{}^T$ [with r values ranging from 0.851 to 0.951 ($n = 10$)]. However, the best correlations of the oxidation

SCHEME 1



potentials of all 2-substituted phenols were those with the solvent parameters, representing the physical properties, namely the f_ϵ [with r values ranging from 0.938 to 0.982 ($n = 10$)] and the β ones [with r values ranging from 0.868 to 0.939 ($n = 10$)]. The above differences could be attributed to the different chemical species involved in the calculation of the two parameters. Moreover, the reasonable correlations found between BDE and/or IE energetic parameters and some experimental solvent ones could allow for an approximate estimation of either one of the former from those of the latter, in different environments, thus saving computational and/or experimental work.

Electronic Effects of the Substituent on the BDE and IE. A deeper insight into the electronic effect of the substituent X on the BDE and IE parameters is presented next. For this, three isodesmic reactions are constructed to characterize the individual energetic terms. The latter concern the stabilization or the destabilization of the parent phenol (SPP) and its respective radical (SPR) and cation radical (SPC), determined by using the isodesmic reactions 1, 2, and 3, respectively (Scheme 1).

In particular, in the case of the BDE, in both the gas and the liquid phase, the total stabilization/destabilization enthalpy is comprised of both the SPP and SPR and is equal to the ΔBDE value (estimated as $\Delta\text{BDE} = \text{BDE}_{2-\text{X}-\text{ArOH}} - \text{BDE}_{\text{PhOH}}$),

$$\Delta\text{BDE} = \text{SPR} - \text{SPP} \quad \text{(Scheme 1, isodesmic reaction 4)}$$

In the case of the IE, in both the gas and the liquid phase, the total stabilization/destabilization energy is comprised of both the SPP and SPC and is equal to the ΔIE value (estimated as $\Delta\text{IE} = \text{IE}_{2-\text{X}-\text{ArOH}} - \text{IE}_{\text{PhOH}}$),

$$\Delta\text{IE} = \text{SPC} - \text{SPP} \quad \text{(Scheme 1, isodesmic reaction 5)}$$

Table 3 summarizes the total stabilization/destabilization effect values, ΔBDE and ΔIE values, along with the SPP, SPR, and SPC ones in the gas phase; the corresponding liquid-phase values for the nine 2-X-ArOH studied are given in Table 4. In both cases, values were evaluated by using the most stable away conformers. The contributions of SPP, SPR, and SPC on the ΔBDEs and ΔIEs and the influence of the medium on the total effects will be studied next, on the basis of the above values.

TABLE 3: B3LYP/6-31+G(,3pd)-Calculated ΔBDE, ΔIE, SPP, SPC, and SPR Values for 2-X-ArOH in the Gas Phase (in kcal/mol)

X	ΔBDE	ΔIE	SPP	SPC	SPR
NO_2	2.8 (2.7)[a]	17.5	7.4	24.9	10.2
CN	1.6 (1.4)	11.9	1.3	13.2	2.9
CF_3	2.6 (1.3)	14.5	3.0	17.5	5.6
CHO	0.9 (0.6)	8.9	0.8	9.7	1.7
COOH	2.1 (1.7)	6.8	5.5	12.3	7.6
Br	−0.7 (−1.2)	0.4	2.5	2.9	1.8
Cl	−0.4 (−1.2)	3.3	3.3	6.6	2.9
F	−0.6 (−1.9)	6.4	4.6	11.0	4.0
CH_3	−1.7 (−2.0)	−6.0	−0.4	−6.4	−2.1
OCH_3	−4.2 (−5.0)	−16.0	4.4	−11.6	0.2
OH	−3.2 (−4.5)	−8.6	4.4	−4.2	1.2
NH_2	−10.1 (−11.4)	−25.3	−0.2	−25.5	−9.9
NMe_2	−11.2 (−10.4)	−36.9	4.2	−32.7	−7.2

[a] Reference 21.

For a comparison to literature data, Table 3 also shows that our gas-phase ΔBDEs are in close agreement with the calculated values of Korth et al.[21] It is also seen that the SPP, SPR, and SPC values in the gas phase are in close agreement with those referring to the apolar solvents; still, values belonging to the same group of solvents are almost identical.

Calculated values, given in Tables 3 and 4, show that in all media, the decreased BDEs (negative ΔBDEs) in the EDG-substituted phenols are the combined result of the radicals stabilization (negative SPRs) and the parents destabilization (positive SPPs). However, the increased BDEs (positive ΔBDEs) in the EWG-substituted phenols seem to be the combination of both the parents and the radicals destabilization. The same conclusions were also drawn recently[14] for some 2-X-ArOH in the liquid phase. In particular, it was shown that the total effect, ΔBDE, is mainly governed by the SPR rather than the SPP effect. However, the latter cannot be ignored,[56,57] because substituents may introduce changes in the ground-state energy

TABLE 4: B3LYP/6-31+G(,3pd)-Calculated ΔBDE, ΔIE, SPP, SPC, and SPR Values for 2-X-ArOH in the Liquid Phase (in kcal/mol)

		group A		group B		group C		
X		*n*-heptane	benzene	acetone	acetonitrile	ethanol	methanol	water
NO_2	ΔBDE/ΔIE	3.5/18.8	3.6/18.4	2.6/18.5	3.9/16.9	3.2/15.6	−0.2/12.1	3.2/15.5
	SPP	6.9	7.0	7.8	6.4	7.5	10.9	7.3
	SPC	25.7	25.4	26.3	23.3	23.1	23.0	22.8
	SPR	10.4	10.6	10.4	10.3	10.7	10.7	10.5
CN	ΔBDE/ΔIE	1.8/12.1	2.1/12.0	2.1/10.8	2.0/10.6	1.1/9.9	1.1/9.8	1.0/9.6
	SPP	1.0	0.9	0.4	0.4	1.7	1.0	0.9
	SPC	13.1	12.9	11.2	11.0	11.6	10.8	10.5
	SPR	2.8	3.0	2.5	2.4	2.8	2.1	1.9
CHO	ΔBDE/ΔIE	1.4/9.9	1.8/11.4	2.3/8.9	2.3/8.9	2.0/7.9	2.0/13.8	2.1/14.0
	SPP	0.7	0.6	0.8	0.8	2.0	2.0	1.9
	SPC	10.6	12.0	9.7	9.7	9.9	15.8	15.9
	SPR	2.1	2.4	3.1	3.1	4.0	4.0	4.0
COOH	ΔBDE/ΔIE	2.5/9.2	2.9/7.6	2.7/9.6	2.4/9.7	2.3/6.7	2.4/6.7	2.3/6.9
	SPP	5.0	4.9	4.3	4.2	4.2	4.1	3.9
	SPC	14.2	12.5	13.9	13.9	10.9	10.8	10.8
	SPR	7.5	7.8	7.0	6.6	6.5	6.5	6.2
Me	ΔBDE/ΔIE	−1.9/−4.4	−1.7/−4.1	−2.3/−3.5	−2.4/−3.4	−4.3/−2.8	−4.3/−2.8	−4.4/−2.7
	SPP	−0.4	−0.6	−0.1	−0.2	−2.1	−2.1	−2.5
	SPC	−4.8	−4.7	−3.6	−3.6	−4.9	−4.9	−5.2
	SPR	−2.3	−2.3	−2.4	−2.6	−6.4	−6.4	−6.9
OMe	ΔBDE/ΔIE	−4.7/−12.8	−4.6/−12.5	−5.4/−10.0	−5.7/−9.6	−6.7/−8.0	−7.0/−8.3	−7.2/−8.0
	SPP	4.3	4.0	3.8	3.7	3.9	4.2	4.1
	SPC	−8.5	−8.5	−6.2	−5.9	−4.1	−4.1	−3.9
	SPR	−0.4	−0.6	−1.6	−2.0	−2.8	−2.8	−3.1
OH	ΔBDE/ΔIE	−4.1/−8.2	−3.8/−7.9	−4.8/−7.4	−5.1/−7.5	−7.1/−7.1	−7.3/−0.3	−7.5/−6.9
	SPP	4.3	4.1	3.9	4.0	5.0	5.0	4.8
	SPC	−3.9	−3.8	−3.5	−3.5	−2.1	4.7	−2.1
	SPR	0.2	0.3	−0.9	−1.1	−2.1	−2.3	−2.7
NH_2	ΔBDE/ΔIE	−10.6/−23.7	−10.3/−23.5	−11.3/−21.8	−11.4/−21.7	−13.4/−20.9	−13.4/−20.7	−13.5/−20.6
	SPP	0.2	0.0	1.3	1.4	3.6	3.6	3.7
	SPC	−23.5	−23.5	−20.5	−20.3	−17.3	−17.1	−16.9
	SPR	−10.4	−10.3	−10.0	−10.0	−9.8	−9.8	−9.8
NMe_2	ΔBDE/ΔIE	−11.6/−33.5	−11.6/−32.1	−12.1/−27.5	−12.3/−29.5	−13.6/−27.1	−13.6/−23.1	−13.5/−26.9
	SPP	4.5	4.4	4.9	4.8	5.8	5.8	5.6
	SPC	−29.0	−27.7	−22.6	−24.7	−21.3	−17.3	−21.3
	SPR	−7.1	−7.2	−7.2	−7.5	−7.8	−7.8	−7.9

of the molecule and bond.[56,58] Hence, it was suggested that[14] both SPR and SPP contributions are decisive in the derivation of the ΔBDE.

It should be noted that the investigation of the total effect, ΔIE, in both the gas and the liquid phase resulted in the same, with respect to the ΔBDE, consideration: the electronic effect of the EDG decreases the values of both parameters in all media, and the opposite holds true for the EWG one. However, a comparison between the SPR and SPC contributions in the ΔBDE[14] and in the ΔIE, respectively, shows that, in the latter case, the SPC contribution is much more the decisive one than that of the SPR in the former case in all media. This could be due to the coexistence of the charge and spin on the cationic radicals, resulting in a greater "sensitivity" toward the electronic effects of the substituents than that in the corresponding radicals. Nevertheless, both SPP and SPC should be taken into account in the total effect on IE, and none of them could be ignored, in agreement with the previous suggestion, concerning the BDE.[14]

Study of the HAT vs SET Mechanisms in the Liquid Phase. In Table 5, the 2-X-ArOH BDE and IE values, derived by selecting the most stable conformer of each species in all media, are compared to phenol (reference compound) and are given in terms of the ΔBDE and ΔIE values. The question of the parallel action of the two free-radical scavenging mechanisms, HAT and SET, is addressed first.

It was suggested[1,4] that the ΔBDE vs ΔIE correlations could be an index of the parallel action of HAT and SET in the vitamin E analogues.[1]

TABLE 5: B3LYP/6-31+G(,3pd)-Predicted ΔBDEs and ΔIEs for 2-X-ArOH in the Gas and Liquid Phases Relative to Phenol (in kcal/mol)

			solvent		
X		gas phase	group A	group B	group C
NO_2	ΔBDE[a]	14.8	13.4	10.2	3.1
	ΔIE[a]	17.0	18.9	19.4	14.3
CN	ΔBDE	3.7	2.8	2.1	1.1
	ΔIE	12.8	12.1	10.7	9.8
CHO	ΔBDE	8.9	8.3	6.9	2.5
	ΔIE	6.1	8.0	9.0	6.6
COOH	ΔBDE	7.2	5.9	3.8	1.0
	ΔIE	3.7	5.9	7.5	8.2
Me	ΔBDE	−1.6	−1.9	−2.4	−4.4
	ΔIE	−6.0	−4.5	−3.5	−2.8
OMe	ΔBDE	−6.7	−5.7	−2.8	−6.5
	ΔIE	−13.5	−10.3	−8.0	−7.8
OH	ΔBDE	−6.8	−6.5	−6.1	−6.8
	ΔIE	−6.6	−6.1	−5.9	−5.7
NH_2	ΔBDE	−10.1	−10.5	−11.3	−13.4
	ΔIE	−25.4	−23.1	−21.4	−20.6
NMe_2	ΔBDE	−7.5	−8.9	−10.6	−13.0
	ΔIE	−36.9	−32.8	−28.5	−25.7

[a] Average values for each particular group of solvents.

Figure 2 presents the ΔBDE vs ΔIE values correlation in the apolar solvents (group A) for which a linear correlation ($\Delta IE = 3.0524\Delta BDE + 4.1170$, $R^2 = 0.9713$) is found. The same picture holds also true for both the gas phase and groups B and C (Figure S3, Supporting Information). In particular, the linear correlation [$y = 3.5409x + 3.5190$] found in the gas phase

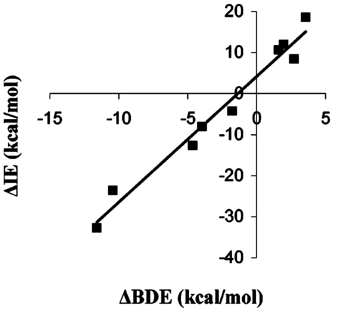


Figure 2. The ΔBDE vs ΔIE values correlation in the apolar solvents (group A).

presents a R^2 value of 0.9527, becoming 0.9784 and 0.9597 in groups B and C, respectively. These values could account well for the assumption of the simultaneous action of both mechanisms in the gas phase (already mentioned by Wright et al.[4]) as well as in the apolar, polar, and/or protic solvents. Due to the absence of corresponding to theoretical and/or experimental data in solution, comparisons cannot be made. The only ΔBDE vs ΔIE correlation found is that in the gas phase,[1] presenting a rather poor R^2 value of 0.67.

The ΔBDE vs ΔIE correlations in the liquid phase are given for the first time as a result of a systematic theoretical study of both BDE and IE at the same level of theory. The satisfactory correlations found between the two parameters in all groups of solvents could (a) verify, in a concrete way, the assumption[1,4] that BDE and IE would be strongly correlated in both the gas and the liquid phase and (b) confirm the parallel action of HAT and SET mechanisms in 2-X-ArOH.

It should be mentioned at this point that usually, an efficient antioxidant activity of a phenolic compound is associated with negative ΔBDE and ΔIE values. However, any molecule with negative ΔBDEs and ΔIEs cannot be considered as an antioxidant. Certainly, this does not mean that the study of compounds with positive ΔBDEs and ΔIEs is meaningless. For instance, the aza-analogue of a-TOH was found to be useless as an antioxidant[39] because, due to the decrease of the IE, it reacts directly with oxygen via SET, (prooxidant activity). In these cases, electron donors could increase the BDE and IE (based upon the additivity rules, valid for the ΔBDE and ΔIE)[4,40] and, hence, improve the antioxidant properties of the compound.

Wright et al.[4] suggested that in the gas phase, for ΔBDE values of ca. −10 kcal/mol and ΔIE up to about −36 kcal/mol, the HAT mechanism dominates. The change from HAT to SET occurs at around ΔIE of ca. −40 kcal/mol and becomes dominant at about −45 kcal/mol.

On the basis of the above criteria and the correct calculated ΔIE and ΔBDE values of the model 2-X-ArOH compounds studied herein, predictions could be made concerning the possible mechanism in the real, large antioxidants. The same values could also help in the rational design of phenolic antioxidants. It also appears that the ΔIE and ΔBDE values of all model 2-X-ArOH compounds will participate, to some extend, in the evaluation of the final corresponding parameter values of a real antioxidant and, hence, to its possible antioxidant mechanism. Certainly, as it was expected, the existence of the EWG leads to a decrease of the antioxidant activity due to the corresponding increase of both ΔIE and ΔBDE values. On the other hand, the change from HAT to SET demands a significant energy difference. Consequently, despite the strong oxidation potential solvent correlation, it seems that the presence of a particular solvent by itself is not sufficient enough for a transition of that kind. The involvement of specific ED and/or EW groups in the 2-X-ArOH appears also to be necessary.

Summary and Conclusions

In this paper, for both the gas and the liquid phase, the bond dissociation enthalpy (BDE) and the adiabatic ionization energy (IE) values of some 2-monosubstituted phenols were calculated by using density functional theory with the B3LYP functional and a 6-31+G(,3pd) basis set. Seven different solvents (*n*-heptane, benzene, acetone, acetonitrile, ethanol, methanol, and water) were used in the calculations, along with a set of 2-X-substituents including four-electron-withdrawing groups ($-NO_2$, −CN, −CHO, and −COOH) and five-electron-donating groups (−Me, −OMe, −OH, $-NH_2$, and $-NMe_2$). Four additional substituents ($-CF_3$, −F, −Cl, and −Br) were also studied in the gas phase.

In both EDG- and/or EWG-substituted species (parent, radical, and/or cation radical), the most stable conformer is varied, depending on the medium and the substitution.

Because, in both the gas and the liquid phase, the EWG substituents increase the O−H BDE of the phenols, whereas the EDG ones decrease it, the former afford a harder hydrogen atom abstraction (hence, a weaker antioxidant activity) than the latter ones. This is also the case with the IEs, presenting however a stronger effect. Moreover, although the liquid-phase BDEs increase with the polarity and the hydrogen-bonding ability of the solvent, the opposite holds true for the oxidation potentials, exhibiting however a stronger effect.

Our gas-phase-calculated IE for benzene is among the most accurate ones in the field, compared to the experiment that for phenol appears as the most accurate one. Our approach provides theoretical BDEs and IEs for the 2-X-ArOH, which are very close to the very few existing experimental ones. Hence, all of the rest IEs and BDEs as well as ΔIEs predicted by us in both the gas and the liquid phase are expected to be accurate to the same extend. Moreover, our calculations verify the assumptions made that the IEs in solution would be (a) highly correlated with the gas-phase ones and (b) strongly solvent dependent.

The electronic effect of the EDG decreases both the ΔIE and ΔBDE parameter values in all media, and the opposite holds true for the EWG one. The SPC contribution is much more the decisive one, in the ΔIE than that of the SPR in the ΔBDE, in all media.

The reasonable correlations found between the ΔBDE and ΔIE could account well for the assumption of the simultaneous action of both mechanisms in both the gas and the liquid phase. It seems that the presence of a particular solvent by itself is not sufficient enough for a HAT to SET transition. The coexistence of specific ED and/or EW groups appears to also be necessary.

It appears that our theoretical approach is not only generally applicable to the set of substituents important to antioxidant activity, but also is useful in (a) the rational design of phenolic antioxidants and (b) affording accurate BDE and IE parameter values, related to both possible antioxidant mechanisms.

Acknowledgment. We thank two anonymous referees and Prof. J. A. M. Simoes for helpful comments.

Supporting Information Available: Table S1, correlations of the BDE and/or IE values with selected solvent parameters. Figure S1, relative enthalpies, ΔH_{rel} with respect to the most stable conformer of the 2-OH−, 2-Me−, $2\text{-}NH_2-$, $2\text{-}NMe_2-$, 2-CN−, 2-CHO−, and $2\text{-}NO_2-ArOH^{\bullet+}$, cation radical conformers in each medium. Figure S2, the ΔBDE vs ΔIE values correlation, in the gas phase and in groups B and C. This material is available free of charge via the Internet at http://pubs.acs.org.

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